EXPERIMENTAL ARTHRITIS

Therapeutic promise of dual blockade of IL-17 and TNF in inflammatory arthritis

The role of tumor necrosis factor (TNF) in the development and progression of rheumatoid arthritis (RA), and the therapeutic benefits of blocking this proinflammatory cytokine, are well established. However, not all patients with RA respond to anti-TNF therapy, indicating that other cytokines are also involved in the inflammation, cartilage damage and joint destruction in this disease. Research from the Netherlands, published in *Arthritis & Rheumatism*, highlights the important role of IL-17 in these processes and the potential therapeutic value of blocking both IL-17 and TNF in an animal model of arthritis.

Several lines of evidence suggest that IL-17 has a key role in the pathogenesis of inflammatory arthritis: this cytokine is expressed in the synovia of patients with RA and in mice with collagen-induced arthritis (CIA), and blockade or genetic neutralization of this cytokine in mice reduces the development and severity of disease. Previously performed *ex vivo* studies, using RA synovial co-cultures, have shown that combined blockade of IL-1, IL-17 and TNF is more effective than blocking TNF alone, but the *in vivo* outcomes of dual blockade of IL-17 and TNF were not known. As Wim van den Berg, the lead researcher on this latest study, explains, “Anti-TNF agents are certainly not sufficient in all RA patients, so there is a need for broader coverage. The anti-TNF and anti-IL-1 antibody combination was unsuccessful because of infection problems, but combining anti-TNF and anti-IL-17, which works independently of IL-1, could be a safer approach.”

First, the authors investigated the effects of overexpressing IL-17 or TNF, or both, in the joints of healthy mice. “We decided to use adenoviral constructs expressing TNF and IL-17, to generate sustained levels of the two cytokines

in the joint,” says van den Berg. “This approach avoids repeated injections and flaws of differences in clearance kinetics.” Histological analyses were performed 4 or 10 days later. Overexpression of both cytokines resulted in considerably higher levels of joint inflammation, cartilage proteoglycan depletion and bone erosion than either cytokine alone; importantly, irreversible cartilage damage (detected as cartilage death and surface erosions) was seen when both cytokines were overexpressed but not after overexpression of either cytokine alone. Further experiments established that this irreversible cartilage damage was not just caused by increased levels of inflammation, but resulted from the synergistic actions of these cytokines in the joint. “Synergy between TNF and IL-17 is not new in terms of inflammation, but the synergy on cartilage erosion described in this paper is novel,” states van den Berg.

Which pathways are switched on when IL-17 and TNF are overexpressed? To answer this question, the authors next analyzed the gene expression profiles of synovial biopsies and isolated cartilage layers to answer this question. The combined overexpression of IL-17 and TNF resulted in considerably increased synovial mRNA levels of the alarmin S100A8 and the cytokine IL-1β, and

cartilage mRNA levels of various matrix metalloproteinases (MMPs), than either cytokine alone. Overexpression of TNF and IL-17 together was also shown to enhance nuclear factor κB activation to a greater extent than overexpression of either cytokine alone. “The synergistic effect is mainly seen on downstream erosion mediators such as S100A8 and MMPs,” explains van den Berg. “The role of the alarmin S100A8 is hot: not only a marker of erosion but a direct erosive mediator!”

Finally, the authors used the CIA model to assess the *in vivo* effects of blocking both TNF and IL-17 in comparison with those of blocking either cytokine alone. Mice treated with anti-TNF antibodies and soluble IL-17 receptor before onset of disease developed milder disease than those treated with control or a single cytokine blocker. In addition, in mice with established disease, blockade of these two cytokines stopped the disease from progressing to the extent seen in mice that received control or in which only one cytokine was blocked. The dual blockade of TNF and IL-17 resulted in reduced inflammation and also reduced cartilage destruction in the recipient mice. “This improved efficacy and additional protection against cartilage erosion is suggestive of a combination therapy in RA patients based on this approach,” concludes van den Berg. “Some companies are actively constructing hybrid molecules with a dual TNF–IL-17 scavenging capacity for this purpose.”

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Original article Koenders, M. I. et al. TNF/IL-17 interplay induces S100A8, IL-1β and MMPs, and drives irreversible cartilage destruction *in vivo*: Rationale for combination treatment during arthritis. *Arthritis Rheum.* doi:10.1002/art.30418

Further reading van Vollenhoven, R. F. Unresolved issues in biologic therapy for rheumatoid arthritis. *Nat. Rev. Rheumatol.* 7, 205–215 (2011)